

The University of Chicago

SOME SUBSTITUTED PYRIMIDINES

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1935

By

EARL RICHARD TWEEDIE

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SOME RESULTS OF RESEARCH

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BY
J. H. VAN VLECK



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INTRODUCTION

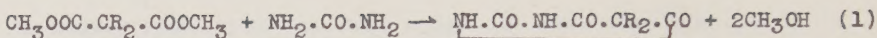
For centuries opium, and more recently derivatives of opium, have been used to deaden pain and to produce stupor or sleep. However, these drugs are toxic and very habit forming. The discovery and development of many synthetic chemicals having a hypnotic action with a minimum of dangerous or disagreeable after-effects has been one of the great achievements of organic chemistry applied to pharmacology.

A great variety of chemical compounds of widely different constitution possess the physiological property of producing hypnosis. At the present time practically all the hypnotics in use are derivatives of urea, which of itself has only a slight sedative action. The modern era of hypnotics began in the year 1903 when E. Fischer¹ prepared Veronal (Barbital, U. S. P.), which is diethylbarbituric acid, NHCONHCOC(C₂H₅)₂CO. Since then there have been synthesized and evaluated pharmacologically more than one hundred barbiturates of relatively similar structure. Since these compounds are all, unfortunately, more or less toxic, research has continued for the preparation of more suitable hypnotic compounds.

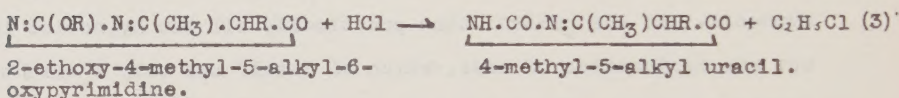
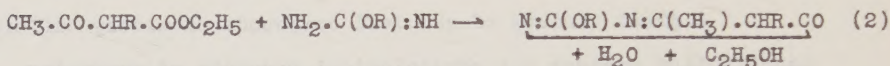
Dialkyl malonic esters, $\text{CRR}(\text{COOCH}_3)_2$, condense readily with urea and with derivatives of urea, such as O-alkyl urea, $\text{NH}_2\text{C}(\text{OR})\text{:NH}$, thiourea, and guanidine, according to the following

¹Ann., 335, 334 (1904).

equation:



Bruce¹ and Stieglitz developed an analogous method for the preparation of alkyl substituted uracils from β -keto esters and their α -alkylated derivatives by condensing them with O-alkyl urea, $\text{NH}_2 \cdot \text{C}(\text{OR}) : \text{NH}$, where R represented an alkyl radical, according to the following equations:



Under the direction of Dr. Stieglitz this method has been used in this laboratory to prepare a large number of substituted uracils. Attempts to prepare 5,5-dialkylated uracils of the formula $\text{HN} \cdot \text{CO} \cdot \text{N} : \text{C}(\text{CH}_3) \text{CRR} \cdot \text{CO}$, by condensing α, α -dialkyl acetoacetic ester, $\text{CH}_3\text{CO} \cdot \text{CRR} \cdot \text{COOC}_2\text{H}_5$, with O-alkyl urea and other urea derivatives have so far proved unsuccessful.

The intensity of the hypnotic action of compounds of the type NHCONHCOCRRCO varies with the number and the nature of the alkyl groups present in the compound.² The theory that ethyl groups have a specific hypnotic action was advanced by Kast and Baumann³ in the year 1890. Later work² has shown that in general the hypnotic action of a compound increases in intensity with the increase in the number of carbon atoms in the alkyl groups substituted in the compound up to C₄ or C₅, and then the hypnotic effect decreases with the increase in size of the substituted groups.

¹Bruce, Doctorate Dissertation, University of Chicago, 1904; J. Am. Chem. Soc., 26, 419 (1904).

²Tabern and Shelburg, J. Am. Chem. Soc., 55, 328 (1933).

³Zeit. physiol. chem., 14, 52 (1890).

The compounds monoethylbarbituric acid, $\text{NHCONHCOCH}(\text{C}_2\text{H}_5)\text{CO}$, and methyl-ethyl barbituric acid, $\text{NHCONHCOC}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CO}$, have only a slight hypnotic action. By substituting an ethyl group for hydrogen in the first compound, and for methyl in the second compound, diethylbarbituric acid, barbital, is formed, which is widely used as a hypnotic.

Phenylethylbarbituric acid (pheno-barbital), $\text{NHCONHCOC}(\text{C}_6\text{H}_5)(\text{C}_2\text{H}_5)\text{CO}$, is very useful as a hypnotic and sedative in the treatment of epilepsy, but its usefulness is impaired by its toxic action. This toxic property is apparently due to the presence of the phenyl group, as the closely related compound, diethylbarbituric acid, is much less toxic. It was thought possible that 4-phenyl-5,5-diethyluracil, $\text{NHCON}:\text{C}(\text{C}_6\text{H}_5)\text{C}(\text{C}_2\text{H}_5)_2\text{CO}$, being similar in structure to pheno-barbital and having one more ethyl group present, might have a more intense hypnotic action and be less toxic than pheno-barbital.

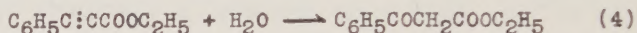
At the suggestion and under the direction of Dr. Stieglitz the present investigation was undertaken to attempt the preparation of 4-phenyl-5,5-diethyluracil. This goal was not attained, experimental difficulties being met which it was not found possible to overcome. In this report the steps taken and the observations made in preparing intermediate products looking toward the above objective, will be presented. Among the intermediate products the following are the most important:

- (1) 2-ethoxy-4-phenyl-6-oxypyrimidine, $\text{N}:\text{C}(\text{OC}_2\text{H}_5)\text{N}:\text{C}(\text{C}_6\text{H}_5)\text{CH}_2\text{CO}$.
- (2) 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine,
 $\text{N}:\text{C}(\text{OC}_2\text{H}_5)\text{N}:\text{C}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_2\text{H}_5)\text{CO}$.
- (3) 2,6-oxy-4-phenyl-5-ethylpyrimidine, $\text{NHCON}:\text{C}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_2\text{H}_5)\text{CO}$.
- (4) 1,5-ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine,
 $\text{C}_2\text{H}_5\text{NC}(\text{OC}_2\text{H}_5):\text{NC}(\text{C}_6\text{H}_5):\text{C}(\text{C}_2\text{H}_5)\text{CO}$.
- (5) 1,5-ethyl-2,6-oxy-4-phenylpyrimidine, $\text{C}_2\text{H}_5\text{NCONHC}(\text{C}_6\text{H}_5):\text{C}(\text{C}_2\text{H}_5)\text{CO}$.
- (6) 2,6-oxy-4-phenyl-5-ethyl-5-bromopyrimidine,
 $\text{NHCON}:\text{C}(\text{C}_5\text{H}_6)\text{CBr}(\text{C}_2\text{H}_5)\text{CO}$.

I. DISCUSSION OF PREPARATIVE METHODS

A. Preparation of Materials

1. Benzoylacetic Ethyl Ester, $C_6H_5COCH_2COOC_2H_5$, was first prepared by Baeyer¹ by the hydration of phenylpropionic ester as indicated in the following equation:



The ester has been prepared in many other ways but most of the methods are unsatisfactory and the yields are low.² Three of the most promising methods were investigated by the author with the view of selecting the most suitable method for the preparation of the ester on a moderately large scale.

Claisen³ developed a method for the preparation of benzoylacetic ethyl ester by the condensation of ethyl benzoate with ethyl acetate in the presence of dry sodium ethylate. He reported a yield of 33 per cent of the ethyl benzoate used, which is equivalent to 26 per cent of the theoretical yield; the ester was collected over a range of ten degrees, 165°-175°, at 20 mm. pressure. Schriner and Schmidt⁴ have stated that all their attempts to duplicate this yield have failed. The condensation was also studied by Marvel and Shiao,⁵ and the best yield obtained by them was

¹Ber., 15, 2705 (1882).

²Perkin, J. Chem. Soc., 45, 1884); Ber., 28, 812 (1895).

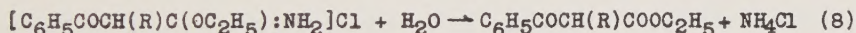
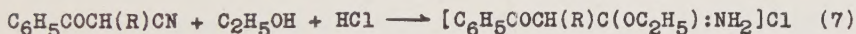
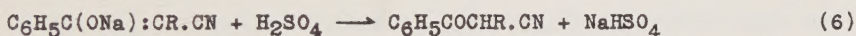
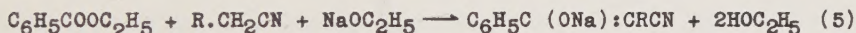
³Claisen and Lowman, Ibid., 20, 653 (1887).

⁴J. Am. Chem. Soc., 51, 3636 (1929).

⁵Thesis, University of Illinois, 1920.

18 per cent of the theoretical yield; frequently no yield was obtained. McElvain¹ made a study of this same method of condensation and reported a yield of 37 per cent of the theoretical yield. Using the same method he condensed ethyl benzoate with ethyl propionate obtaining a yield of 19 per cent of the theoretical yield of α -methyl benzoylacetic ethyl ester, $C_6H_5COCH(CH_3)COOC_2H_5$. The author's yield of benzoyl acetic ester by this method ranged from 6 per cent to 20.8 per cent of the theoretical.

McElvain¹ also developed a method for the preparation of the β -keto esters by the hydrolysis of the imino ester hydrochlorides, $[C_6H_5COCH(R)C(OC_2H_5):NH_2^+]\bar{Cl}$, obtained from the corresponding α -benzoylalkyl cyanides, $C_6H_5CO\cdot CHR\cdot CN$, by the condensation of ethyl benzoate with the cyanides by means of sodium ethylate. The method is indicated by the following reactions:



The yields of the alkyl benzoylacetic ethyl ester, $C_6H_5COCH(R)COOC_2H_5$, ranged from 35 per cent to 44 per cent of the theoretical yields. This method was not investigated.

Claisen² developed a second method for the preparation of benzoylacetic ethyl ester which was easier to carry out than the first method, and which gave consistently good yields, ranging from 34.3 per cent to 48.9 per cent of the theoretical. The sodium salt of benzoylacetoacetic ethyl ester, $C_6H_5C(ONa):C(COCH_3)COOC_2H_5$,

¹J. Am. Chem. Soc., 54, 2960 (1932).

²Ann., 291, 67 (1896).

was prepared by the addition of one mol of benzoyl chloride to a solution of one mol of acetoacetic ethyl ester in absolute ethanol which contained two mols of sodium ethylate. Benzoylacetic ethyl ester was obtained from the sodium salt by breaking off the acetyl group through saponification. After considerable experimentation this method was finally adopted as the most reliable method tried.

Schriner and Schmidt¹ investigated this method of preparation of benzoylacetic ester and reported that attempts by several workers to duplicate Claisen's yield of 64 per cent to 67 per cent of the theoretical gave yields of only 29 per cent to 34 per cent of that required by the theory; the ester being collected over a range of four degrees. Schriner and Schmidt modified the method and reported a yield 58 per cent of the theoretical yield. They benzoylated acetoacetic ester in a medium of dry benzene, metallic sodium being used as the condensing agent. This method was tried and found to be unsatisfactory; it was difficult to remove the excess of benzoyl chloride used, and, on distillation of the benzoylacetoacetic ethyl ester, a rather large quantity of benzoic acid was formed. The best yield obtained by the author, using this method, was 38.5 per cent of the theoretical.

2. Ethylation of Benzoylacetic Ethyl Ester.--Benzoylacetic ethyl ester is readily converted into α -ethyl benzoylacetic ester, $C_6H_5COCH(C_2H_5)COOC_2H_5$, with good yield,² by treatment in alcoholic solution with sodium ethylate and an excess of ethyl iodide.³ The excess of ethyl iodide (75 per cent-100 per cent)

¹Loc. cit.

²Perkin, J. Chem. Soc., 45, 182 (1884).

³See p. 32.

is easily recoverable.

α,α -Diethyl benzoylacetic ethyl ester, $C_6H_5COC(C_2H_5)_2COOC_2H_5$, cannot be prepared by treatment of the α -ethyl benzoylacetic ester with sodium ethylate and ethyl iodide in an alcoholic solution. It is prepared¹ from α -ethyl benzoylacetic ester in a toluene solution, by treatment first, with finely divided sodium, and then with ethyl iodide. α,α -Dialkyl benzoylacetic esters are insoluble in dilute alkalis, while the monoalkyl derivatives are gradually hydrolyzed and dissolved in a 3 per cent aqueous potassium hydroxide. When the mixture of mono- and di-alkyl benzoylacetic ester, obtained by the ethylation process, was shaken with 3 per cent aqueous potassium hydroxide for two days a separation of the two esters was obtained. The method of ethylation is unsatisfactory and the yields are very low; Perkin's best yield being only 20 per cent of the theoretical yield. Perkin ascribes this low yield to the relative inactivity of ethyl iodide. In support of this view he cites the fact that the yield of α,α -methylethyl benzoylacetic ester, $C_6H_5COC(CH_3)(C_2H_5)COOC_2H_5$, is greater when methyl iodide reacts in toluene solution with the sodium derivative of α -ethyl benzoylacetic ester than when ethyl iodide reacts, under the same conditions, with the sodium derivate of α -methyl benzoylacetic ester. He also points out that benzyl chloride reacts with the sodium derivative of α -ethyl benzoylacetic ester to give a 60 per cent yield of α,α -ethylbenzyl benzoylacetic ester, $C_6H_5COC(C_6H_5CH_2)(C_2H_5)COOC_2H_5$. It should be pointed out, however, that α -ethyl acetoacetic ester is readily ethylated by ethyl

¹Perkin, J. Chem. Soc., 95, 2048 (1909).

iodide in an alcoholic solution, giving good yields of α,α -diethyl acetoacetic ester. Folkers and Adkins¹ have developed a method for methylation in toluene which gives a 71 per cent yield of α -methyl acetoacetic ethyl ester and a 54 per cent yield of α,α -dimethyl acetoacetic ester,² the yields being based on the quantities of esters used.

3. O-Ethyl Urea, $\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{NH}$.--The simple O-alkyl ureas, also known as alkyl isoureas, were first prepared by McKee³ under the direction of Stieglitz, and studied at length by McKee⁴ and by Bruce.⁵ They have been used extensively in this laboratory for condensation with β -keto esters to form substituted uracils.

In the present investigation the method of Stieglitz and McKee, as modified by Basterfield⁶ and later by Terre,⁷ was used for the preparation of O-ethyl urea from cyanamide. Calcium cyanamide is used for the preparation of cyanamide.⁸ The method is very satisfactory, giving yields of 85 to 90 per cent of the calculated yields, the O-ethyl urea being obtained in the form of its hydrochloride, $[\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{NH}_2]\text{Cl}$. The free base was prepared by the method described by McKee⁹ and modified by

¹J. Am. Chem. Soc., 53, 1406 (1931).

²Solkowski, J. Pr. chem., 2 106, 255 (1923). 66.7 per cent yield.

³Am. Chem. J., 26, 209 (1901).

⁴Ibid.

⁵J. Am. Chem. Soc., 26, 419 (1904).

⁶Doctor's Dissertation, University of Chicago, 1920.

⁷Master's Dissertation, University of Chicago, 1932.

⁸Basterfield, loc. cit.

⁹Loc. cit.

Basterfield.¹

B. Condensations with O-Ethyl Urea

Bruce² found that O-alkyl ureas condense very readily with β -keto esters to form pyrimidines according to the following equation:



α -Substituted acetoacetic esters, $\text{CH}_3\text{CO}\cdot\text{CHR}\cdot\text{COOC}_2\text{H}_5$, will not condense with urea,³ but will condense with O-alkyl ureas, which are much stronger bases than urea, being of about the same order of strength as ammonia.⁴ However, all attempts to condense O-alkyl ureas with α,α -diethyl acetoacetic ester, $\text{CH}_3\text{CO}\cdot\text{C}(\text{C}_2\text{H}_5)_2\text{COOC}_2\text{H}_5$, have thus far failed. Since dialkylmalonic esters, $\text{RO}\cdot\text{COCRR}\cdot\text{CO}\cdot\text{OR}$, readily condense with O-ethyl urea, it was thought that α,α -dialkyl benzoylacetic esters, $\text{C}_6\text{H}_5\text{CO}\cdot\text{CRR}\cdot\text{COOC}_2\text{H}_5$, in which the negative phenyl group has been substituted for the negative RO group, might likewise condense with O-alkyl ureas.

The condensation reaction was carried out in the usual way. A white precipitate was obtained which was insoluble in chloroform, slightly soluble in alcohol and readily soluble in dilute alcohol and in water. The compound was not examined further, since Lowe's⁵ investigation with dialkylacetoacetic esters indicated that such condensations formed compounds of the type $\text{CH}_3\text{CO}\cdot\text{CR}_2\text{CO}\cdot\text{N:C(OR)}\cdot\text{NH}_2$.

¹Basterfield, loc. cit.

²Bruce, loc. cit.

³Behrend, Ann., 229, 16 (1885).

⁴Bruce, loc. cit.

⁵Unpublished work.

Bruce¹ carried out the condensation of O-alkyl ureas with β -keto esters by warming a mixture of the two compounds at 50° to 60° for about an hour, or by allowing the mixture to stand for a few days. He obtained a yield of about 90 per cent of the theoretical of 2-methoxy-4-methyl-6-oxypyrimidine, $N:C(OCH_3)N:C(CH_3)-CH_2CO$, by warming a mixture of O-methyl urea and acetoacetic ethyl ester at 50° for a few minutes. Basterfield² reported a yield of 2-ethoxy-4-methyl-6-oxypyrimidine, $N:C(OC_2H_5)N:C(CH_3)-CH_2CO$, of 90 to 93 per cent of the theoretical. The yields obtained by condensing O-alkyl urea with α -alkyl acetoacetic ester, $CH_3COCHRCOOC_2H_5$, have not been reported. Metzner³ obtained yields of about 25 per cent of the theoretical yield of 2-ethoxy-4-methyl-5-ethyl-6-oxypyrimidine, $NHC(OC_2H_5)N:C(CH_3)CH(C_2H_5)CO$, by condensing O-ethyl urea with α -ethyl acetoacetic ester.

Basterfield stated that prolonged heating of condensation mixtures of O-ethyl urea and malonic methyl ester gave poorer yields than were obtained by warming the mixture slightly and allowing it to stand in a desiccator for a few days. He also found that malonic methyl ester gave a better yield than malonic ethyl ester did.

The experience of other workers⁴ has confirmed Basterfield's observation that prolonged heating of the condensation mixture reduces the yield. Lowe carried out the condensation by allowing the condensation mixture to stand for five or six days in a desiccator over sulphuric acid and solid potassium hydroxide, the desiccator being evacuated the fourth day. The solid material

¹Loc. cit.

²Loc. cit.

³Unpublished work.

⁴Bartholomew, loc. cit.

which had formed was then collected on a filter, washed with dry, alcohol-free ether and recrystallized from hot alcohol. Lowe stated that better yields were obtained by this method than were obtained by heating the condensation mixture.

My results confirmed those of Lowe. I prepared a mixture of α -ethyl benzoylacetate ethyl ester (1 mol) and O-ethyl urea (1.15 mol) and divided it into three portions. One portion, contained in a stoppered Erlenmeyer flask, was placed inside a steam-bath and heated by the live steam. Within twenty minutes crystals began to separate from the oil. At the end of an hour the flask and contents were placed in a desiccator over sulphuric acid and solid potassium hydroxide and left for two days. Very little increase in the amount of solid matter present was observed at the end of two days. The solid material was collected on a filter and was washed with dry ether. From this solid material only a very small amount of 2-ethoxy-4-phenyl-5-ethyl 6-oxypyrimidine, $N:C(OC_2H_5)N:C(C_6H_5)CH(C_2H_5)CO$, was obtained. The yield of 2,6-oxy-4-phenyl-5-ethyl pyrimidine, obtained by the procedure described later, was about 12 per cent of the theoretical.

The second portion of the mixture was heated in a stoppered flask on top of the steam bath for an hour and then placed in a desiccator for two days. The first yield of crude material amounted to 9.3 per cent of the theoretical yield. A second yield, obtained by replacing the filtered oil in a desiccator for four days, brought the total yield of crude material up to 18.6 per cent of the theoretical. The third portion of the mixture was placed in a desiccator over sulphuric acid and solid potassium hydroxide without being warmed. This mixture was allowed to stand for five days, the desiccator being evacuated on the fourth day. The first yield of crude material amounted to 26.4 per cent of the

theory. A second yield of 3.3 per cent was obtained after twelve more days, making the total yield obtained by this method 29.7 per cent of the calculated yield. The yields of the crude material are given for comparison, since so much difficulty was experienced in obtaining the desired pyrimidines from this crude product.¹

Baskerfield² condensed malonic methyl ester with O-ethyl urea and obtained a compound which he at first thought to be malonyldiethyl-di-O-ethyl urea, $\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{N}\cdot\text{COCH}_2\text{CO N}:\text{C}(\text{OC}_2\text{H}_5)\text{NH}_2$, but he later concluded this was an O-ethyl urea salt of 2-ethoxy barbituric acid, $\text{NH}\cdot\text{C}(\text{OC}_2\text{H}_5):\text{N}\cdot\text{CO CH}:\text{CONH}_2:\text{C}(\text{OC}_2\text{H}_5)\text{NH}_2$. On being treated with cold dilute hydrochloric acid this compound was immediately converted into 2-ethoxy barbituric acid, $\text{NHC}(\text{OC}_2\text{H}_5):\text{N}\cdot\text{CO}\cdot\text{CH}_2\text{CO}$, and O-ethyl urea hydrochloride. Barbiturates and pyrimidines containing the group $-\text{CH}_2\text{CO}-$, or $-\text{CHR}\cdot\text{CO}-$ are weak acids due to the enolization of these groups into the acid forms, $-\text{CH}:\text{COH}$ and $-\text{CR}:\text{COH}$. They dissolve in dilute alkalis and are reprecipitated by acids. Warmington³ states that phenyl uracil, $\text{NH}\cdot\text{CO}\cdot\text{NH C}(\text{C}_6\text{H}_5):\text{CH}:\text{COH}$, is a very weak acid, since it dissolves in dilute alkali and is reprecipitated by carbon dioxide.

When O-alkyl ureas, which are moderately strong bases, are condensed with β -keto esters to form pyrimidines, salts of the type $\text{N}:\text{C}(\text{OC}_2\text{H}_5)\text{N}:\text{C}(\text{CH}_3)\text{CH}:\text{C}\bar{\text{O}}[\text{NH}_2\text{C}(\text{OC}_2\text{H}_5)\cdot\text{NH}_2^+]$ may be formed. Bruce did not mention this salt formation in the condensations he carried out with O-alkyl ureas. Basterfield used an excess of acetoacetic ester mixed with O-ethyl urea and obtained high yields of 2-ethoxy-4-methyl uracil with no salt formation. Con-

¹See p. 14 for the method of purification.

²Loc. cit.

³Loc. cit.

condensing O-ethyl urea with malonic methyl ester and with oxalic ethyl ester he obtained large yields of O-ethyl urea salts of 2-ethoxy-barbituric acid and of ethoxy-parabanic acid. Other investigators¹ in this laboratory have indicated that in condensing O-alkyl urea with β -keto esters salt formation occurred. In view of these facts the crude product obtained by condensing O-alkyl ureas with β -keto esters, after being washed with dry ether, is placed in alcohol and treated with hydrochloric acid until the mixture is neutral or very slightly acid. The strong hydrochloric acid combines with the O-alkyl urea, thus liberating the weak pyrimidine acid.

Working with α -ethyl benzoylacetic ethyl ester, $C_6H_5COCH(C_2H_5)COOC_2H_5$, and O-ethyl urea the author experienced great difficulty in obtaining 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine, $N:C(OC_2H_5)N:C(C_6H_5)CH(C_2H_5)CO$ (m.p. 156° - 157°), from the crude condensation product. After considerable work three compounds were isolated from the crude product and converted into 2,6-oxy-4-phenyl-5-ethyl pyrimidine, $NHCO N:C(C_6H_5)CH(C_2H_5)CO$, (m.p. 211° - 212°). The crude condensation product was washed with dry ether, boiled with a small quantity of alcohol and the mixture filtered while hot. The filtrate, on cooling, yielded a small amount of ethoxy pyrimidine (m.p. 156°), which is quite soluble in alcohol. The undissolved portion of the crude product was then boiled with a fairly large quantity of alcohol and the solution filtered while hot. From this filtrate crystals were obtained which, after recrystallization from boiling alcohol and drying in a desiccator over sulphuric acid, finally melted at 241° - 242°

¹Lowe, loc. cit.
Bartholomew, loc. cit.
Terre, loc. cit.

with decomposition. This compound is slightly soluble in cold water, the solution being strongly alkaline. It was recrystallized from boiling water, much of the material remaining in solution when the water was cooled. These crystals, dried for half an hour over a steam radiator, melted at about 239° , showing that the compound is not appreciably hydrolyzed by boiling water. On the addition of hydrochloric acid to the aqueous filtrate, obtained in recrystallizing the material from hot water, a heavy precipitate was instantly formed. This precipitate, after drying, melted at 156° and was found to be 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine. The compound melting at 241° is very soluble in cold dilute hydrochloric acid. After standing for a few minutes crystals separated from the acid solution and were found to be identical with the ethoxy pyrimidine (m.p. 156°). When the hydrochloric acid solution of the compound was boiled a product was obtained which melted at 211° . This was identified as 2,6-oxy-4-phenyl-5-ethyl pyrimidine, $\text{NH}\cdot\text{CO}\cdot\text{N}:\text{C}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_2\text{H}_5)\text{CO}$. When the compound (m.p. 241°) was heated at 80° - 90° in a stream of dry hydrogen chloride a gas evolved which burned with the characteristic green flame of ethyl chloride, the ethyl chloride having been lost in the manner characteristic of O-alkyl urea derivatives.¹ The solid residue, recrystallized from boiling alcohol, melted at 211° and was identical with the 2,6-oxypyrimidine. The ethoxy pyrimidine (m.p. 156°) and the oxypyrimidine (m.p. 211°) were obtained from the compound melting at 241° in still another way. The compound (m.p. 241°) was dissolved in a very little warm sodium hydroxide. The cooled sodium hydroxide solution was neutralized with hydrochloric acid and the ethoxy pyrimidine

¹McKee and Stieglitz, loc. cit.

(m.p. 156°) precipitated. When the sodium hydroxide solution was treated with an excess of hydrochloric acid and the mixture boiled the oxypyrimidine (m.p. 211°) was obtained. From a study of these reactions and from the results of the analyses given below it was concluded that the compound melting at 241° is, either (I) the O-ethyl urea salt of 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine, $\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)C(C}_2\text{H}_5\text{):C}\ddot{\text{O}}[\text{NH:C(OC}_2\text{H}_5\text{)NH}_2^+]$, or (II) the urea salt of the ethoxypyrimidine, $\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)C(C}_2\text{H}_5\text{):C}\ddot{\text{O}}[\text{NH}_3^+\text{CONH}_2]$. Micro-analyses by Pregl's methods gave the following results:

Calculated for I, $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_3$; C, 61.4; H, 7.28; N, 16.86.

Calculated for II, $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_3$; C, 59.2; H, 6.58; N, 18.4.

Found (Ave. of three analyses): C, 58.97; H, 7.13; N, 20.35.

The very considerable portion of the crude condensation product which is insoluble in hot alcohol does not melt at 350°. Since the oxypyrimidine is obtainable from this compound by the method described below the compound is considered to be either compound I or II (above) or the salt of ethoxypyrimidine with some other basic component. It was boiled with dilute hydrochloric acid, forming a solution from which crystals separated on cooling. These crystals, which did not melt at 351°, dissolved readily in warm water producing a strongly acid solution. On recrystallization of this compound from boiling water, most of it was converted into 2,6-oxy-4-phenyl-5-ethylpyrimidine (m.p. 211°). It was not studied further, since the desired pyrimidine could be obtained from it.

In practice the crude condensation product of O-ethyl urea and α -ethyl benzoylacetic ethyl ester was boiled with dilute hydrochloric acid and thus converted directly into 2,6-oxy-4-phenyl-5-ethylpyrimidine.

C. N-Ethylation of 2-Ethoxy-4-Phenyl-5-Ethyl Pyrimidine

The hydrogen atoms attached to each nitrogen atom of uracil, $\text{NH}^1\cdot\text{CO}^2\cdot\text{NH}^3\text{C}^4(\text{CH}_3):\text{CH}_2^5\text{CO}^6$, can be replaced with alkyl or substituted alkyl groups.¹ If only one group is substituted it usually enters in the 1-position, the nitrogen in that position being more acidic² than the nitrogen in position 3. In some cases mixtures of N-1 and N-3 substitution products are formed. Behrend and Dietrich³ found that when potassium methyluracil is treated with methyl iodide, under various conditions, a mixture of dimethyluracil, trimethyluracil and unchanged methyluracil is obtained. The formation of 3,4-dimethyluracil is favored by methylating dry potassium methyluracil with methyl iodide at 140°, while 1,4-dimethyluracil is the chief product formed when the methylation is carried out in an aqueous or alcoholic potassium hydroxide solution of methyluracil. Evans and Johnson⁴ methylated 4-phenyluracil in methanol, using metallic sodium and an excess of methyl iodide; they obtained a yield of 20 per cent of 1-methyl-4-phenyluracil, $\text{CH}_3\text{NCONHC}(\text{C}_6\text{H}_5)\text{CHCO}$, and 30 per cent of 1,3-dimethyl-4-phenyluracil, $\text{CH}_3\text{NCON}(\text{CH}_3)\text{C}(\text{C}_6\text{H}_5):\text{CHCO}$, the yields being based on the amount of phenyluracil used. No trace of 3-methyluracil was found. Davidson and Baudisch⁵ methylated an aqueous sodium hydroxide solution of uracil with methyl sulphate, obtaining a yield of 94 per cent of the theoretical yield of 1,3-dimethyluracil.

Hilbert and Johnson⁶ developed a new method for alkylating

¹Evans and Johnson, J. Am. Chem. Soc., 52, 4993 (1930).

²Hilbert and Johnson, ibid., p. 2001.

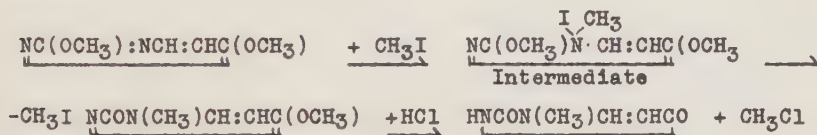
³Ann., 309, 265 (1899).

⁴Loc. cit.

⁵J. Am. Chem. Soc., 48, 2379 (1926).

⁶Loc. cit.

pyrimidines of the uracil type in the 3-position. They found that pyrimidines of the structure of 2,6-dialkoxy-pyrimidines, $\text{NC(OR):NCH:CHC(OCH}_3\text{)}$, and 2-oxy-3-alkyl-6-alkoxy-pyrimidines, $\text{NCON(CH}_3\text{)CH:CHC(OC}_2\text{H}_5\text{)}$, easily undergo rearrangement on being heated to form 1,3-dialkyluracils, $\text{CH}_3\text{NCON(CH}_3\text{)CH:CHCO}$, in excellent yields. A partial rearrangement was not found possible by heat, but by action of alkyl iodides a partial rearrangement takes place smoothly at room temperature, according to the following representation:



By this process the alkylation always takes place in position 3, the nitrogen atom in that position, according to Johnson, being more basic than the nitrogen atom in position 1.

2-Ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine, $\text{N:C(OC}_2\text{H}_5\text{)N:C-(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO}$ (m.p. 156°), was ethylated in absolute ethanol by the use of an equivalent quantity of metallic sodium and an excess of ethyl iodide; a yield of 24 per cent of the theoretical yield of 1,5-ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine, $\text{C}_2\text{H}_5\text{NC(C}_2\text{H}_5\text{):NC(C}_6\text{H}_5\text{)C(C}_2\text{H}_5\text{)CO}$ (m.p. 70°), was obtained. This N-ethyl pyrimidine is extremely soluble in all the ordinary organic solvents and in dilute hydrochloric acid. There being no hydrogen available for the formation of an enol-compound the N-ethyl pyrimidine is not acidic and does not dissolve in warm dilute sodium hydroxide. The compound is easily de-ethylated by being boiled with dilute hydrochloric acid; 1,5-ethyl-2,6-oxy-4-phenylpyrimidine, $\text{C}_2\text{H}_5\text{NCON:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO}$ (m.p. 164.5°), is formed. This oxy-N-ethylpyrimidine is much less soluble in organic solvents than is

the ethoxy compound. It dissolves readily in warm dilute sodium hydroxide, but not in warm dilute hydrochloric acid.

The "dialzo" color test, developed by Johnson and Clapp,¹ was used to determine the position of the N-substituted ethyl group in 1,5-diethyl-2-ethoxy-4-phenyl-6-oxypyrimidine. Uracils, with the exception given below, develop an intensely red color when treated with diazobenzenesulphonic acid and then with a little aqueous sodium hydroxide. Johnson and Clapp state that " . . . the formation of red colors is entirely prohibited by substitution in the 3-position in uracil. . . . It is also of interest to note here that 6-oxypyrimidine, HNCH:NCH:CHCO, and 6-amino-pyrimidine, NCH:NCH:CHC·NH₂, do not give a red color with diazobenzenesulfonic acid. Whether this reagent reacts to form colored compounds only with pyrimidines having a -CONH- grouping in the 1,2 or 2,3 positions must be decided by further experiments."

The "dialzo test" was applied by Terre¹ to a number of N-ethylated 5-ethyl pyrimidines and found to be dependable. When the "dialzo test" was applied to 1,5-diethyl-2-ethoxy-4-phenyl-6-oxypyrimidine no red color developed, indicating, apparently, that the substituted ethyl group was in position 3. It was suspected, however, that the ethoxy group in position 2 might be preventing the development of the red color. So the test was applied to 1,5-ethyl-2,6-oxy-4-phenylpyrimidine, which immediately developed a red color. This reaction was taken as proof that the ethyl group is substituted in position 1.

To further test the inhibiting action of the ethoxy group

¹J. Biol. Chem., 5, 165 (1909).

²Loc. cit.

in position 2 the test was applied to two other ethoxy compounds and their de-ethylated derivatives. In each case¹ the 2-ethoxy compounds failed to give a red color while their 2-oxy derivatives developed intensely red colors. The results of these tests support the supposition of Johnson and Clapp that only those pyrimidines having a -CONH- grouping in the positions 1,2 or 2,3 develop a red color when subjected to the "diazo test."

D. Bromination of 2,6-Oxy-4-Phenyl-5-Ethylpyrimidine

Uracil (2,6-oxypyrimidine) is easily brominated when it is suspended in carbon disulphide and treated with an excess of bromine.² After this mixture is allowed to stand for two days the carbon disulphide is evaporated off and the residue is recrystallized from hot water, giving a good yield of 5-bromouracil, NHCONHCH:CBBr·CO. Using this same method Metzner³ obtained good yields of 2,6-oxy-4-methyl-5-ethyl-5-bromopyridine, NHCON:C(CH₃)-CBBr(C₂H₅)CO. Johnson⁴ obtained a yield of 6.9 g. of 3-methyl-4-phenyl-5-bromo-4,5-dihydrouracil, HNCON(CH₃)CH(C₆H₅)CH(Br)CO, by heating in a sealed tube 5 g. of 3-methyl-4-phenyl-4,5-dihydrouracil, dissolved in chloroform, with an excess of bromine.

E. Fischer⁵ obtained 85 per cent yields of 4-phenyl bromhydrouracil by the same method using glacial acetic acid as the solvent. Johnson⁶ also obtained 1,3-diethyl-5-bromouracil, C₂H₅NCON(C₂H₅)CH:CBBrCO, by adding the required amount of bromine

¹See p. 42.

²Wheeler, Am. Chem. J. 29, 486 (1903).

³Unpublished work.

⁴J. Am. Chem. Soc., 52, 4993 (1930).

⁵Fischer, Ber., 34, 3762 (1901).

⁶J. Am. Chem. Soc., 52, 2001 (1930).

to 1,3-diethyl uracil dissolved in absolute alcohol.

Considering the ease with which the various uracils mentioned are brominated, it was surprising to find that 2,6-oxy-4-phenyl-5-ethylpyrimidine (m.p. 211° , $\text{HNCON:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO}$, should be difficult to brominate. It was suspended in carbon disulphide, and also in carbon tetrachloride, and was shaken for five days with an excess of bromine; in each case the original pyrimidine was recovered. The same result was obtained when the mixtures were heated in glass-stoppered bottles on the steam bath for five hours and then shaken for five days. Exposing the mixture to diffused sunlight (in December) for several days had no effect. An attempt was made to brominate the pyrimidine by the heating of a solution of the compound in chloroform with an excess of bromine for one hour at 100° in a sealed tube. The pyrimidine was recovered unchanged. A glacial acetic solution of the pyrimidine with an excess of bromine was heated in a bomb at 100° for six hours, the bromine color being only slightly changed. Most of the pyrimidine (m.p. 211°) was recovered unchanged. A small amount of material melting at 185° - 188° gave a positive Beilstein test for halogens. The material was not examined further. Attempts to brominate 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine were likewise unsuccessful. The addition of an aqueous solution of bromine to a solution of the ethoxy-pyrimidine in dilute sodium hydroxide resulted in the production of a mixture of the ethoxy pyrimidine and its de-ethylated derivative 2,6-oxy-4-phenyl-5-ethylpyrimidine.

When aromatic hydrocarbons containing a side-chain are brominated in direct sunlight, in intense electric light, or at their boiling point, substitution of bromine in the side-chain is favored. A modification of this method was finally applied to

the bromination of 2,6-oxy-4-phenyl-5-ethylpyrimidine, which can be considered a derivative of benzene, $C_6H_5C:C(C_2H_5)CONHCONH$. When a suspension of the pyrimidine in hot carbon tetrachloride, contained in a glass-stoppered bottle, was shaken with an excess of bromine under the influence of a 500 watt electric light, the bromine was rapidly absorbed and hydrogen bromide evolved. The crude product obtained by this reaction was found to be a mixture of unchanged pyrimidine, pyrimidine hydrobromide, monobromopyrimidine and monobromopyrimidine hydrobromide. The hydrobromides decompose with evolution of hydrogen bromide when heated at 120° to 130° . When the bromination was carried out in a three-necked flask fitted with a dropping funnel, a mechanical stirrer and a reflex condenser, considerable hydrogen bromide escaped through the condenser, and smaller quantities of hydrobromides were formed.¹

An attempt was made to determine the position of the bromine atom in the bromopyrimidine by the oxidation of the compound with potassium permanganate² in an alkaline solution. A compound which melted at 130° - 135° with decomposition was isolated from the oxidation mixture. A qualitative analysis showed the presence of nitrogen and bromine in the compound. Micro-analysis of the compound gave the following result: Calculated for $NH_2CONHCOC_6H_4Br$ ($C_8H_7O_2N_2Br$); N, 11.52. Found: N, 11.52. Several attempts to analyse the compound for bromine by the use of

¹Bruce prepared 2-ethoxy-4-methyl-6-oxypyrimidine hydrochloride, $Cl[HN:C(OC_2H_5)N:C(CH_3)CH_2CO]$, by passing dry hydrogen chloride into a solution of the pyrimidine in dry benzene. He also prepared 2-ethoxy-4-methyl-5-ethyl-6-oxypyrimidine hydrochloride by evaporating to dryness a solution of the pyrimidine in hexa-normal hydrochloric acid.

²Behrend, *Ann.*, 323, 178 (1902); *Ann.*, 353, 267 (1907). Johnson and Flint, *J. Am. Chem. Soc.*, 53, 1082 (1931). Terre, *loc. cit.*

Parr's micro-bomb were unsuccessful as the material did not fuse properly. The compound is very soluble in alcohol, soluble in dilute sodium hydroxide and insoluble in ether. No trace of benzoyl urea was found.

According to the work of Behrend¹ and Terre² oxidation of the bromopyrimidine at room temperature should produce benzoyl-urea (m.p. 214°) if the bromine is in the pyrimidine ring, or bromobenzoylurea (m.p. not known) if the bromine is in the benzene nucleus:



If the compound melting at 130° to 135° is bromobenzoylurea³ it should give a bromobenzoic acid by hydrolysis with hydrochloric acid. The small amount of material (m.p. 130°-135°) available was refluxed for two hours with concentrated hydrochloric acid. From this reaction a few milligrams of material were obtained which melted partly at 155° and completely at 167°. Metabromobenzoic acid melts at 155°.

If the bromo-compound is 2,6-oxy-4-phenyl-5-ethyl-5-bromopyrimidine, NHCON:C(C₆H₅)CBr(C₂H₅)CO, oxidation of the compound in a sodium hydroxide solution would produce sodium bromide. No bromine was found in the inorganic residue obtained from the oxidation mixture.

Although the conditions under which the bromination was

¹Loc. cit.

²Loc. cit.

³Ortho and meta-bromobenzanilides melt at a lower temperature than does benzanilide.

Benzanilide, C ₆ H ₅ NHCOC ₆ H ₅	m.p. 160°-161°.
O-bromobenzanilide, C ₆ H ₅ NHCOC ₆ H ₄ Br	m.p. 123°.
M-bromobenzanilide, C ₆ H ₅ NHCOC ₆ H ₄ Br	m.p. 137°.

carried out favor substitution in the side chain the evidence presented above seems to indicate that bromine was substituted in the nucleus forming 2,6-oxy-4-bromophenyl-5-ethylpyrimidine,

NHCON:C(C₆H₄Br)CH(C₂H₅)CO.

II. EXPERIMENTAL PART

A. The Experimental Materials

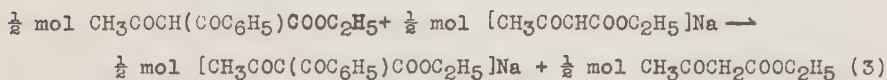
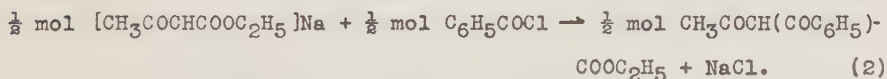
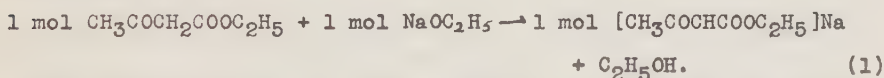
1. Benzoylacetic Ethyl Ester, $C_6H_5COCH_2COOC_2H_5$.--Of the methods for preparing benzoylacetic ethyl ester described in the literature (see p. 4), the three most promising were tried. Claisen's second method was finally selected as the most reliable. The following are the details of the three methods as carried out.

a. Claisen's First Method.¹ A two liter three-necked flask was fitted with a reflux condenser, a mercury sealed stirrer, and a 500 cc. dropping funnel. The apparatus was dried for three hours over an electric hot-plate, while dry, oxygen-free nitrogen was passed slowly through it. Dry sodium ethylate (140 g. or 1 mol) was prepared in the three-necked flask in a stream of dry nitrogen; ethyl benzoate (300 g. or 1 mol) was then added to the sodium ethylate, and the whole heated on a steam-bath until it began to solidify into a brown-colored mass. An excess of ethyl acetate (350 g.) was added to the mixture which was well stirred and refluxed for fifteen hours. Following this, the mixture was cooled and glacial acetic acid (150 g.) added to it. The addition of the acetic acid caused a thick, almost solid mass to form. Water was added to the mixture until the latter was completely decomposed with the liberation of a considerable amount of oil. The water layer was separated from the oil layer and extracted

¹Ber., 20, 653 (1887).

with ether. The ether extract was combined with the oil and washed with dilute sodium carbonate and then with water. The ether was removed, the residual oil dried in a desiccator over solid potassium hydroxide and then fractionated under reduced pressure. Yields of 26 g. and 35 g. (166°-176° at 20-22 mm. pressure) and 80 g. (150°-159° at 15-16 mm. pressure) were obtained. They represent a yield of only 6.8 per cent to 20.8 per cent of theory, whereas Claisen reported a yield of 100 g. boiling between 165° and 175° at 20 mm. pressure, or 33 per cent of the ethyl benzoate used and equivalent to a yield of 26 per cent of the theoretical. Moreover it was found very difficult to break up the sodium ethylate which formed a hard cake in the bottom of the flask, and its reaction with the ethyl benzoate was incomplete. On distilling the rather large amount of oil obtained (about 500 cc.) considerable quantities of ethyl acetate and ethyl benzoate were recovered, while a large amount of a resinous mass of dehydrobenzoylacetic acid, $\text{C}_6\text{H}_5\text{COCOCH}(\text{COC}_6\text{H}_5)\text{COCH}$, remained.

b. Claisen's¹ Second Method.--This method was found to be very satisfactory, the yields being consistently good.² The method of preparation is indicated in the following series of reactions:



¹Ann., 291, 67 (1896).

²See p. 29, Table I.

By this series of reactions $\frac{1}{2}$ mol of sodium benzoylacetoacetic ethyl ester is formed and $\frac{1}{2}$ mol of acetoacetic ester remains. This process is then repeated, in each case with one-half of the first amounts used, that is, $\frac{1}{2}$ mol of sodium ethylate is now added to the mixture and followed by the addition of $\frac{1}{4}$ mol of benzoyl chloride. This process is continued until altogether one mol of benzoyl chloride and a second mol of acetoacetic ester have been used in the reaction.

The method was carried out in the following way: A two liter three-necked flask was fitted with a mercury-sealed stirrer, a reflux condenser and a 500 cc. dropping funnel. The condenser and the funnel were each fitted with a calcium chloride tube. The apparatus was dried for three hours over an electric hot-plate in a current of dry air. Sodium ethylate was prepared in this flask from 300 cc. of absolute ethanol and 17.7 g. (1 mol) of sodium. A similar solution of sodium ethylate was prepared in a dry one liter flask. Pure, dry acetoacetic ethyl ester (100 g. or 1 mol) was added to the sodium ethylate in the three-necked flask, and the mixture cooled to 5°. The condenser was then removed and a burette, fitted with a calcium chloride tube, and charged with benzoyl chloride, was put in its place. The flask was kept in ice water so that the temperature of the mixture could not mount above 10° or 12°. During vigorous stirring 45 cc. of benzoyl chloride ($\frac{1}{2}$ mol) was added from the burette to the mixture over a period of fifteen minutes. A fine yellow precipitate formed. At this point Claisen's directions were slightly modified. He allowed the mixture to stand for thirty minutes, then added (with stirring) 150 cc. ($\frac{1}{2}$ mol) of the second solution of sodium ethylate and followed this immediately by the addition of a second quantity of benzoyl chloride. Since the reaction

mixture is a thick syrupy mass, it seemed best to continue the stirring after each addition of benzoyl chloride, so that the reaction expressed in equation (2) above might be more certainly completed. Likewise, after the addition of the 150 cc. of sodium ethylate, the mixture was stirred for five minutes before beginning the addition of the second portion of benzoyl chloride. If benzoyl chloride is added to the mixture before the reaction shown in equation (3) above is completed, a considerable amount of ethyl benzoate may be formed. After the addition of the 150 cc. ($\frac{1}{2}$ mol) of sodium ethylate, as mentioned above, the mixture was stirred for five minutes, and then a second portion of benzoyl chloride (22.5 cc., $\frac{1}{4}$ mol) was added to the mixture during a period of ten minutes. The stirring was continued for another twenty minutes, and then 75 cc. ($\frac{1}{4}$ mol) of sodium ethylate was added to the contents of the flask. A very efficient stirrer was required, since the reaction material forms a thick jelly-like yellow mass. A glass stirrer with one blade was found to be more satisfactory than the usual two-bladed stirrer. The alternate addition of benzoyl chloride and sodium ethylate was continued until 90 cc. (1 mol) of benzoyl chloride and all of the second solution of sodium ethylate (1 mol) had been used. The mixture was then allowed to stand at room temperature for about twelve hours. It was filtered through a large Buchner funnel, and the very stable, yellow crystalline salt was washed with ether. If a large quantity of ether is used, an additional amount of the salt is precipitated from the filtrate. To recover all the yellow salt requires the addition of so much ether that the recovery is not economically justified.

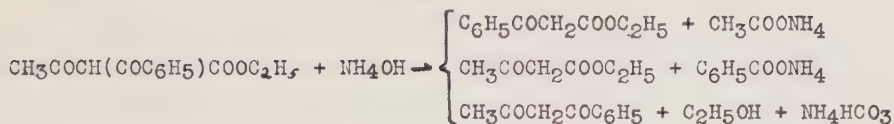
From 200 g. of the acetoacetic ester Claisen obtained 424 g. of the yellow precipitate, which consisted of about 80 g.

of sodium chloride, the balance being the sodium salt of benzoylacetoacetic ethyl ester, representing a yield of 90 per cent of the theoretical yield. The above experiment gave a yield of 404 g. of the yellow salt, or 85.3 per cent of the theoretical yield. This yield does not include the salt recoverable from the filtrate by the addition of ether.

The sodium salt of benzoylacetoacetic ester can be obtained in a pure form by solution of the crude product in the least possible amount of absolute alcohol, the mixture being warmed for a short time on the steam bath, and the sodium chloride being removed finally by filtration. On standing beautiful yellow crystals separate from the filtrate. To obtain the free benzoylacetoacetic ester the crude salt is dissolved in three times its weight of water, and acetic acid is added to the solution, with cooling, as long as an oil is separated. The oily portion is extracted with ether, the ether extract is washed with water and dried over calcium chloride. On evaporation of the ether the ester is obtained as a colorless oil.

Benzoylacetic ethyl ester can be obtained from the crude sodium salt of benzoylacetoacetic ester. It is dissolved in water in the proportion of 40 g. of the salt to 100 cc. of water. To this solution is added 9 g. of ammonium chloride and 25 cc. of a 10 per cent ammonium hydroxide solution. The mixture is kept at 40° for ten minutes, with vigorous stirring, and then cooled in ice water. The ether extract of this mixture is washed with water, dried over calcium chloride, and then fractionated at a reduced pressure.

The hydrolysis must be carefully adjusted to get the desired product, since it may take any of the following courses:



The following yields, averaging 40.7 per cent of the theoretical yields, were obtained.

Table I

Aceto-acetic ester	Yellow Salt	Benzoyl-acetic-ester	Yield per cent of Theory	B. Pt.	P. m. m.
100 g.	202 g.	60 g.	40.6%	148°-151°	10-12 mm.
150	275	76	34.3	147°-154°	10-11
150	300	87	39.3	146°-147°	10-11
150	285	77	35	150°-151°	12-13
150	300	95.5	43.9	145°-146°	10-11
150	300	108.5	48.9	153°-155°	13-14
143	290	98	46.7	144°-145°	9-10
Schriner and Schmidt			29-34	4° range	
Claisen					
150	318		64-66		

The yields given in column 4 represent the percentage in reference to the theoretical yields. These yields do not include the amounts obtained by combining the higher and lower boiling fractions and re-distilling them. Neither do they include the amounts of the yellow salt recoverable from the filtrate by the use of large quantities of ether.

The following boiling points of benzoylacetic ethyl ester are given for comparison:

Mayer, <u>Ann.</u> , 347, 78	148°-149°, 12 mm.
Bernhardt, <u>Ann.</u> , 282, 155	147°-149°, 10-12 mm.
Claisen, <u>Ber.</u> , 20, 653	165°-175°, 20 mm.
Claisen, <u>Ann.</u> , 291, 71	159°-165°, 18 mm.
Schmidt, <u>J.A.C.S.</u> , 51, 3636	165°-169°, 20 mm.

c. Schriner and Schmidt's Method.--Schriner and Schmidt obtained yields of only 29 per cent to 34 per cent of the theoretical yield by Claisen's second method. They modified it in the

following way and reported yields of 58 per cent of the theoretical yield. A three liter three-necked flask was fitted with a stirrer, a reflux condenser and a 200 cc. dropping funnel. The condenser and the funnel were fitted with calcium chloride tubes. One mol of acetoacetic ethyl ester and one mol of sodium, cut into small pieces, were added to 2.25 liters of dry benzene, and the mixture was stirred and refluxed for twenty-four hours. The mixture was then cooled and 1.25 mol of benzoyl chloride was added to it over a period of ninety minutes; the mixture was then refluxed with stirring for eight more hours. To the cooled mixture 250 g. of cracked ice was added, and the whole was shaken vigorously for some time. The benzene layer, which contains the benzoylacetoacetic ester, was separated from the water layer, and the benzene was distilled off. The residue was fractionated and the fraction boiling at 177° to 171° (20 mm.) collected. A yield of benzoylacetoacetic ethyl ester of 74.8 per cent of the theoretical yield was obtained. Careful saponification of this ester gave a yield of 58 per cent of the theoretical yield of benzoylacetic ethyl ester, based on the amount of the acetoacetic ester used.

This method was found to be unsatisfactory, since, even with prolonged shaking with ice water, it was difficult to remove the excess of benzoyl chloride present, and on distillation of the benzoylacetoacetic ester large quantities of benzoic acid passed over, clogging the condenser. The best yield of benzoylacetic ester obtained by this method was 38.5 per cent of the theoretical yield, collected over a range of ten degrees.

Claisen's second method was selected as the best of the three methods tried, for the preparation of larger quantities of benzoylacetic ester.

Benzoylacetic ester is a colorless oil sparingly soluble in water, but miscible in all proportions with ether and alcohol. Boiling concentrated potassium hydroxide converts the ester into organic acids, boiling dilute potassium hydroxide forms a ketone:



When a drop of ferric chloride solution is added to a solution of the ester in dilute alcohol, a blood red color is formed. The ester can be identified by its condensation with phenyl hydrazine to form 1,3-diphenyl pyrazolon,¹ $\text{C}_6\text{H}_5\text{N} \cdot \text{N}:\text{C}(\text{C}_6\text{H}_5) \cdot \text{CH}_2\text{CO}$: Equivalent quantities of benzoylacetic ethyl ester and phenyl hydrazine are mixed and allowed to stand until the mixture becomes turbid by the separation of water. Ether is then added to the mixture, and the mass of crystals which form is brought onto a filter and washed with ether. After recrystallization from hot ethanol the compound melts at 137°.

2. α-Ethyl Benzoylacetic Ethyl Ester, $\text{C}_6\text{H}_5\text{CO} \cdot \text{CH}(\text{C}_2\text{H}_5) \cdot \text{COOC}_2\text{H}_5$.--Perkin's² method was used for preparing α-ethyl benzoylacetic ethyl ester. The quantities of materials used and the yields obtained are shown in Table II. The method of procedure used follows: Benzoylacetic ethyl ester (50 g. or 1 mol) was added to an equivalent quantity of sodium ethylate, dissolved in 200 cc. of absolute ethanol; the solution was treated with an excess of ethyl iodide (75 g. or 1.9 mol), the whole being refluxed on the steam bath until a drop of the solution diluted with water was no longer alkaline. If, instead of refluxing, the mixture was allowed to stand over night at room temperature, the

¹Knorr and Klotz, Ber., 20, 2546 (1887).

²J. Chem. Soc., 45, 182 (1884); 95, 2047 (1909).

reaction could be completed by warming the mixture for a few minutes. When the reaction was completed the alcohol and the excess of ethyl iodide were distilled off, the ethyl iodide being recovered by the addition of a large volume of water to the distillate. Water was added to the cooled ester residue and the mixture extracted several times with ether. The extract was washed with water and dried over calcium chloride, the ether removed and the residue fractionated under reduced pressure. The distillation was carried out in a Claisen's distilling flask the upper part of which was wrapped with asbestos paper. The flask was placed in an oil bath which was kept at a temperature 15° to 20° higher than the boiling point of the ester. The distilling flask was fitted with a fine capillary tube, reaching nearly to the bottom of the flask. By this method Perkin obtained a yield of 60 per cent of the calculated yield.

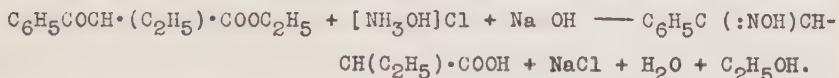
The following yields, averaging 66.4 per cent, were obtained:

Table II

Benzoyl acetic ester	Sodium g.	Alcohol cc.	Iodide cc.	Excess of Iodide	Yield g.	% of Theo. Yield	B. Pt.	P.
20 g.	2.4 g.	60 cc.	28 g.	75%	18.2 g.	79.5	155°-156°	12-13 mm.
50	6	150	60	50	30.5	57	154°-155°	10 mm.
					1.5		151°-154°	10 mm.
50	6	200	75	87	38.5	67.2	154°-157°	13 mm.
89	10.6	270	135	90	68.4	67.1	153°-153°	11-12 mm.
98	11.8	290	125	57	69	61.3	145°-148°	7-8 mm.
Perkin								
5	0.6	15	10	150		60		

α -Ethyl benzoylacetic ethyl ester, $C_6H_5CO \cdot CH(C_2H_5) \cdot COOC_2H_5$, is a colorless, pleasant-smelling oil. When a drop of ferric

chloride solution is added to a solution of the ester in dilute alcohol a muddy-red color is formed instead of the blood-red color formed by benzoylacetic ester under the same conditions. The ester can be identified by the formation of the oxime of the acid:



The oxime is prepared¹ according to the following directions: The ester (1 g. or 1 mol) is dissolved in a little alcohol and 2 g. (4 mol) of potassium hydroxide, dissolved in about 15 cc. of water, is added to it; hydroxylamine hydrochloride (0.48 g. or 0.75 mol) is dissolved in 5-10 cc. of water and added to the mixture. The whole is then warmed slightly and allowed to stand about thirty minutes. Dilute hydrochloric acid is added to the cooled mixture and the white precipitate which forms is separated from the filtrate. It is redissolved in the least possible amount of dilute sodium hydroxide. The oxime is reprecipitated by carbon dioxide passed into the solution; it is brought on a filter, washed with a little water and dried. It melts at 89°-90°.

3. α,α-Diethyl Benzoylacetic Ethyl Ester, $\text{C}_6\text{H}_5\text{COC}(\text{C}_2\text{H}_5)_2\text{COOC}_2\text{H}_5$.--α,α-Diethyl benzoylacetic ethyl ester cannot be prepared by the usual method of ethylation with sodium ethylate and ethyl iodide in an alcoholic solution (see p. 7). It was prepared according to the directions of Perkin.² Sodium (2.3 g. or 1 mol) was added to 65 cc. of dry toluene in an Erlenmeyer flask. The toluene was heated until the sodium melted and the whole was then shaken vigorously to reduce the sodium to the form of fine

¹Hantzsch, Ber., 26, 1691 (1893).

²J. Chem. Soc., 95, 2047 (1909).

pellets. This mixture was cooled and 22 g. (1 mol) of α -ethyl benzoylacetic ethyl ester was added to it. A fairly vigorous reaction set in at first and the solution became light red in color. The reaction soon slowed down and then the mixture was kept warm for three hours. At the end of that time the deep red toluene solution was decanted from the residual sodium into a 300 cc. flask, 20 g. (1.35 mol) of ethyl iodide was added to the solution and the whole refluxed, under an air condenser, for three hours. The flask and its contents were then cooled and an equal volume of ether was added to the mixture. This mixture was shaken with water containing dilute hydrochloric acid, the water layer was removed and extracted with ether. The ether extract was treated with dilute hydrochloric acid and then washed with water. The toluene-ether layer was washed well with water, combined with the ether extract and the whole dried over calcium chloride. The ether and the toluene were removed by evaporation, leaving a reddish-colored oil which was distilled under reduced pressure, yielding 14 g. of a clear oil (collected from 145° to 160°, at 9-10 mm. pressure). This oil, consisting of a mixture of unchanged α -monoethyl benzoylacetic ethyl ester and α,α -diethyl benzoylacetic ester, was shaken for forty-five hours with 175 cc. of a 3 per cent aqueous solution of potassium hydroxide. At the end of that time the unchanged diethyl ester was separated from the hydrolyzed monoethyl ester by extraction of the mixture with ether. The ether extract was washed with water till neutral to litmus, dried over calcium chloride, and fractionated under reduced pressure. The fraction boiling at 155°-160° (8-10 mm.) was collected. The yield was 2.2 g. of α,α -diethyl benzoylacetic ethyl ester, or 8.9 per cent of the theoretical amount. Perkin obtained a yield of 20 per cent of the theoretical,

the ester being collected at 179°-183° at a pressure of 20 mm. The ester gives no color reaction when it is dissolved in dilute alcohol and treated with a drop of ferric chloride.

4. O-Ethyl Urea, $\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{NH}_2$.-- O-ethyl urea was prepared in the form of the hydrochloride, $[\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{NH}_2]\text{Cl}$, according to the directions of Stieglitz and McKee,¹ and also by this method as modified by Stieglitz and Terre.² Yields of 85-90 per cent of the calculated yield were consistently obtained. The pure O-ethyl urea hydrochloride melted at 122° with decomposition. After the decomposition³ the melt solidified and remelted at 131°, the melting point of urea being 132°. McKee's method as modified by Basterfield⁴ was used to prepare the free base.

B. Condensations with O-Ethyl Urea

1. 2-Ethoxy-4-Phenyl-6-Cxypyrimidine, $\text{N:C}(\text{OC}_2\text{H}_5)\text{N:C-}(\text{C}_6\text{H}_5)\cdot\text{CH}_2\text{CO}$.--Benzoylacetic ethyl ester was mixed with an excess of O-ethyl urea and placed in a desiccator over sulphuric acid and solid potassium hydroxide. Since no solid had formed within eighteen hours, the mixture was warmed on a steam-bath for a few minutes and then replaced in the desiccator. Within another twenty-four hours crystals began to form and at the end of five days the mixture appeared to be almost solid. The desiccator was then evacuated and the condensation allowed to continue for another day or two. The solid was collected on a filter and washed with dry ether. The filtrate was replaced in the desiccator in vacuo and left for several days. A second yield of crystals

¹Am. Chem. J., 26, 217 (1901).

²Master's Thesis, University of Chicago, 1932.

³ $\text{NH}_2\text{C}(\text{OC}_2\text{H}_5):\text{NH}_2 \text{ Cl} \longrightarrow \text{NH}_2\text{CONH}_2 + \text{C}_2\text{H}_5\text{Cl}$.

⁴Doctor's Dissertation, University of Chicago, 1920.

brought the total yield of crude product up to 24.1 per cent of the theoretical yield. The crude product was recrystallized from boiling ethanol, hydrochloric acid having been added to the slightly alkaline mixture until it was neutral. After the fine, white, needle-like crystals had been removed from the cooled solution a further yield of the pyrimidine was obtained by the addition of a large volume of water to the filtrate. The crystals, dried in a desiccator over sulphuric acid, melted sharply at 169°-170°.

2-Ethoxy-4-phenyl-6-oxypyrimidine is readily soluble in alcohol, acetone, chloroform, warm dilute hydrochloric acid and in warm dilute sodium hydroxide, moderately soluble in hot carbon tetrachloride and almost insoluble in ether. Micro-analysis by Pregl's methods gave the following results: Calculated for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.59; N, 12.96. Found: C, 65.4; H, 5.49; N, 13.16.

2. 2,6-Oxy-4-Phenylpyrimidine, $HNCON:C(C_6H_5)CH_2CO$.--When 2-ethoxy-4-phenyl-6-oxypyrimidine is boiled for a few minutes with dilute hydrochloric acid (1:3) ethyl chloride is evolved and 2,6-oxy-4-phenylpyrimidine precipitates from the solution. The same result was obtained by passing dry hydrogen chloride over the ethoxy-pyrimidine heated to 80° or 90°. The gas evolved was collected in an azotometer over 50 per cent aqueous potassium hydroxide. It burned in air with a green flame. The oxypyrimidine, recrystallized from boiling water, was obtained in the form of white needle-like crystals which melted at 262°. It is readily soluble in warm alcohol, acetic acid and boiling water; difficultly soluble in chloroform, benzene and cold water. It is amphoteric being soluble in warm dilute acids and alkalis.

Warminton¹ prepared this compound by heating a mixture of benzoylacetic ethyl ester (18 g.) and urea (8 g.) at 170° in a test tube, obtaining a yield of 3.5 g. of phenyluracil (2,6-~~oxy~~-4-phenylpyrimidine), or 20 per cent of the calculated amount. He also prepared phenylthiouracil, HNCSN:C(C₆H₅)CH₂CO, by heating a mixture of benzoylacetic ethyl ester and thiourea at 170°. The phenylthiouracil was dissolved in dilute alkali and phenyluracil was then obtained by neutralizing the solution with acid. By this method he obtained a yield of phenyluracil of 30 per cent of the benzoylacetic ester used, or 30.8 per cent of the theoretical. Johnson and Hemingway² prepared phenylthiouracil by condensing benzoylacetic ester with thiourea in absolute alcohol, using sodium ethylate as the condensing agent and obtaining a yield of 73 per cent of theory. The phenylthiouracil (m.p. 269°-270°) was quantitatively desulphurized by digesting it for a few hours with chloroacetic acid.

3. 2-Ethoxy-4-Phenyl-5-Ethyl-6-Oxypyrimidine, N:C(OC₂H₅)N:
C(C₆H₅)CH(C₂H₅)CO.--To condense β -keto-esters with O-alkyl ureas Bruce³ warmed a mixture of the two compounds at 60° for about one hour. Lowe,⁴ working with acetoacetic ethyl ester and its α -alkyl derivatives, found that better yields were obtained by allowing a mixture of the ester and alkyl urea to stand for five days in a desiccator over sulphuric acid and solid potassium hydroxide. 2-Ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine was prepared according to the directions of Lowe. α -Ethyl benzoylacetic ethyl ester is

¹J. Pr. Chem. (2), 47, 203 (1893).

²J. Am. Chem. Soc., 37, 380 (1915).

³Loc. cit.

⁴Unpublished work.

placed in an Erlenmeyer flask, mixed with a 10 to 20 per cent excess of O-ethyl urea and placed in a desiccator over sulphuric acid and solid potassium hydroxide. On the fourth day the mixture is stirred, the desiccator evacuated and the mixture again allowed to stand for another day or two. The thick, pasty mass which has formed is then stirred with several volumes of dry, alcohol-free ether, and the mixture filtered by means of a syphon filter, care being taken to prevent the absorption of moisture. The ether filtrate is placed on a steam-bath until the major portion of the ether is evaporated; it is then placed in the desiccator, under partial vacuum, over sulphuric acid. After the ether is entirely removed by evaporation the desiccator is evacuated and the material left standing for five or six days; a second yield of crystals is thus obtained. The solid material remaining in the Erlenmeyer after the ether is syphoned off, is washed with dry ether and collected on a filter. This crude product consists of a mixture of three products described in the theoretical part of this thesis.¹ To 5 g. of the crude material about 100 cc. of alcohol are added and the mixture is made slightly acid with dilute hydrochloric acid. The mixture is boiled and then filtered while hot. From the cooled filtrate a mass of white, needle-like crystals is obtained. The mother-liquor is reduced in volume to about one-third, cooled and poured into several times its volume of cold water. The crystals obtained in this way are very fine, long needles having the appearance of cotton wool. The dried crystals melt at 156°-157°. From 40 to 60 per cent of the crude material is insoluble in hot alcohol and has a melting point above 351°. This portion is converted into the oxypyrimidine

¹See p. 13.

when it is boiled with dilute hydrochloric acid as described below.¹

2-Ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine (m.p. 156°-157°) is readily soluble in alcohol, acetic acid, chloroform, hot water and in warm dilute acids and alkalis; almost insoluble in cold water, carbon tetrachloride and ether. It is easily converted into the oxypyrimidine by boiling dilute hydrochloric acid. Micro-analysis of the ethoxy derivative gave the following results: Calculated for $C_{14}H_{16}O_2N_2$: C, 68.82; H, 6.55; N, 11.47. Found: C, 68.85, 69.31; H, 6.74, 6.84; N, 11.41, 11.34.

4. 2,6-Oxy-4-Phenyl-5-Ethylpyrimidine, $HNCON:C(C_6H_5)-CH(C_2H_5)CO$.--2,6-Oxy-4-phenyl-5-ethylpyrimidine is prepared when 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine is boiled with dilute hydrochloric acid (1:3) for ten or fifteen minutes. The crystals of the ethoxypyrimidine gradually go into solution in the hot acid and then after a few minutes new crystals suddenly form. A further yield is obtained by evaporation of the mother-liquor to a small volume. The compound can be recrystallized from hot alcohol or boiling water. The pure crystals melt at 211°-212°. The oxypyrimidine is also obtained from that portion of the crude condensation product which is insoluble in hot alcohol² by means of a small quantity of boiling dilute hydrochloric acid. In this case much of the material remains in solution in the hot acid. The crystals obtained from the cooled acid solution do not melt at 350°. They are readily soluble in hot water, producing a strongly acid solution. When this substance is recrystallized from boiling water the oxypyrimidine melting at 211°-212° is

¹See p. 39.

²See p. 38.

obtained. The compound (m.p. $350^{\circ}+$) seems to be a salt of hydrochloric acid and the oxypyrimidine. The whole of the crude condensation product was usually converted into the oxypyrimidine by boiling dilute hydrochloric acid and recrystallization of the product from boiling water. 2,6-Oxy-4-phenyl-5-ethylpyrimidine is soluble in hot water, alcohol, acetic acid and chloroform; insoluble in cold water, ether and carbon tetrachloride. It is also readily soluble in warm dilute acids and alkalis. Micro-analysis of the compound gave the following results: Calculated for $C_{12}H_{12}O_2N_2$: C, 66.64; H, 5.59; N, 12.96. Found: C, 65.03; H, 5.68; N, 12.94, 12.80.

C. Ethylation of 2-Ethoxy-4-Phenyl-5-Ethyl-6-Oxypyrimidine

1. 1,5-Ethyl-2-Ethoxy-4-Phenyl-6-Oxypyrimidine, $C_2H_5NC(OC_2H_5):NC(C_6H_5):C(C_2H_5)CO$.--1,5-ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine was prepared according to the general method of Lowe. Sodium ethylate is prepared in a 200 cc. flask from 0.31 g. (1.1 mol) of sodium and 50 cc. of absolute ethanol. To this solution 3 g. (1 mol) of 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine and 2.9 g. (1.5 mol) of ethyl iodide are added and the whole is refluxed until a drop of the mixture diluted with water is no longer alkaline. The alcohol and excess of ethyl iodide are distilled off and water is added to the cooled residue which is then extracted with ether. The brownish colored oil, obtained by evaporation of the ether extract, is dissolved in a little warm alcohol and the solution made slightly acid with hydrochloric acid. Water is added to this solution until the mixture becomes slightly milky in appearance. It is then warmed a little until a clear solution is obtained, a few drops of alcohol being added if necessary, and left standing for some time; white, lustrous, needle-like crystals separate from the solution. Their

melting point is 70°. A yield¹ of 0.8 g., or 24 per cent of the calculated yield of 1,5-ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine was obtained. The pyrimidine is extremely soluble in cold alcohol, carbon tetrachloride, chloroform, acetone, ether, benzene and dilute hydrochloric acid, insoluble in warm dilute sodium hydroxide and warm water. Micro-analysis gave the following results: Calculated for $C_{16}H_{20}O_2N_2$: N, 10.32. Found: N, 10.37, 10.47.

2. 1,5-Ethyl-2,6-Oxy-4-Phenylpyrimidine, $C_2H_5NCON:C(C_6H_5)CH(C_2H_5)CO$.- 1,5-ethyl-2,6-oxy-4-phenylpyrimidine is obtained when the ethoxy-pyrimidine is boiled with dilute hydrochloric acid. The ethoxy-pyrimidine (m.p. 70°) melts at first and then gradually is converted into a solid. Recrystallized from boiling alcohol, the latter gave rosettes of white, plate-like crystals which melted at 164.5° and on analysis gave the following results: Calculated for $C_{14}H_{16}O_2N_2$: N, 11.47. Found: N, 11.27, 11.37. The compound is soluble in chloroform, alcohol, acetone and warm dilute sodium hydroxide, insoluble in warm dilute hydrochloric acid, benzene and carbon tetrachloride.

The position of the ethyl group substituted in 2-ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine was determined by the application of the "Diazo Test" as developed by Johnson and Clapp.² Diazo-benzenesulphonic acid was prepared according to the directions of Pauly.³ Two grams of finely powdered sulphanilic acid were shaken with 3 cc. of water and 2 cc. of concentrated hydrochloric acid. One gram of potassium nitrite, dissolved in 1 to 2 cc. of

¹Evans and Johnson, loc. cit.

²J. Biol. Chem., 5, 165 (1909).

³Zeitschr. f. physiol. chem., 42, 516.

water, was added to the mixture in small portions, the mixture being shaken and cooled after each addition. The thick precipitate of diazobenzenesulphonic acid was collected on a filter, washed with a little water and dried. To carry out the "Diazo Test" 5-10 mg. of the pyrimidine is thoroughly mixed with a little less than an equal weight of the sulphonic acid on a dry watch glass. A drop of 10 per cent sodium hydroxide solution is then allowed to flow into the mixture. Under these conditions a red color develops immediately with compounds which react to this test. The test was applied to the following compounds with results as indicated below:

Table III

Compound	Color Reaction
2-Ethoxy-4-phenyl-6-oxypyrimidine, $\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)CH}_2\text{CO}$	Yellow color*
2,6-Oxy-4-phenylpyrimidine, $\text{HNCON:C(C}_6\text{H}_5\text{)CH}_2\text{CO}$	Red color
2-Ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine, $\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO}$	Yellow color
2,6-Oxy-4-phenyl-5-ethylpyrimidine, $\text{HNCON:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO}$	Intense red
1,5-Ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine, $\text{C}_2\text{H}_5\text{NC(OC}_2\text{H}_5\text{):NC(C}_6\text{H}_5\text{):C(C}_2\text{H}_5\text{)CO}$	Yellow color
1,5-Ethyl-2,6-oxy-4-phenylpyrimidine, $\text{C}_2\text{H}_5\text{NCONHC(C}_6\text{H}_5\text{):C(C}_2\text{H}_5\text{)CO}$	Red color

*Diazobenzenesulphonic acid itself gives a yellow color when treated with aqueous sodium hydroxide.

In the present instance the test shows that the ethoxy group in position 2 inhibits the formation of a red color, and that the ethyl group in the N-ethylated pyrimidine is not substituted in position 3.

D. Bromination of 2,6-Oxy-4-Phenyl-5-Ethylpyrimidine

1. 2,6-Oxy-4-Phenyl-5-Ethyl Bromopyrimidine, $\text{NHCON:C(C}_6\text{H}_5\text{)C(Br)(C}_2\text{H}_5\text{)CO}$ ---After many unsuccessful efforts (see p. 20) the bromopyrimidine was finally prepared according to the following directions: 3.85 g. (1 mol) of 2,6-oxy-4-phenyl-5-ethylpyrimidine was finely powdered and suspended in 300 cc. of carbon tetrachloride contained in a glass-stoppered 500 cc. bottle. To this mixture was added 4.3 g. (1.5 mol) of bromine. The bottle was securely stoppered and placed in a shaking machine. A 500 watt electric light was placed within five or six inches of the reaction mixture, and a vigorous shaking of the mixture was maintained until the color of the bromine had disappeared. With the electric bulb placed within six inches of the bottle, the bottle and contents became quite hot and the reaction was completed within thirty or forty minutes. When the electric bulb was placed at twelve inches from the reaction bottle two hours were required for the completion of the reaction. The bottle was removed from the shaking machine, placed in the hood and cautiously opened. The mixture in the bottle was rapidly filtered with the aid of suction through a small Buchner funnel. A yellow solid (5.1 g.) was obtained; after thorough drying, it melted with vigorous foaming at 110° to 130° , then solidified and remelted with decomposition at 215° - 225° . A portion of the yellow substance was shaken with water, and, although the substance was not appreciably soluble, the water became strongly acidic. The material was suspended in water, neutralized with dilute ammonium hydroxide, boiled for a few minutes and the solid collected on a filter, washed with water and dried. The white powder obtained by this process did not produce acidity when shaken with water nor did it melt with foaming and resolidify. It melted with decomposition at 220° - 230° . By a

method of purification described later in this paper¹ this substance was obtained in a pure form (dec. p. 250°) and proved to be a monobromopyrimidine. A sample of the yellow solid was placed in a small test tube and heated in an oil-bath at 130°-140°. A vapor was given off which fumed in moist air, and turned moist blue litmus paper red. The vapor produced a precipitate with silver nitrate solution. The precipitate was soluble in ammonium hydroxide and reprecipitated when the solution was acidified with nitric acid. From a study of the above reactions it was concluded that the yellow substance¹ consisted largely of a monobromopyrimidine, $C_{12}H_{11}O_2N_2Br$, and the monobromopyrimidine hydrobromide, $C_{12}H_{11}O_2N_2Br \cdot HBr$.

Since the hydrobromides are quite soluble; the pyrimidine is moderately soluble; and the bromopyrimidine is insoluble in cold chloroform, the yellow solid was finally purified in the following way: It was triturated for a few minutes with about 20 cc. of cold chloroform and then collected on a filter. The filtrate was removed and the solid was first washed with warm chloroform, to remove the unchanged pyrimidine, and then with a little ether. From 5.1 g. of substance one gram of solid material was obtained which melted at 233°. The chloroform filtrate³ was slowly poured into a large volume of ligroin (b.p.

¹See p. 45.

²When one equivalent, or only a slight excess of bromine was used for bromination, a yellow substance which melted at 120°-130° with effervescence, resolidified and melted with decomposition at 216°-220°, was obtained. This substance was warmed with a small amount of water for a few minutes, treated with dilute ammonium hydroxide until the mixture was neutral and then brought on a filter. The white solid obtained in this way was recrystallized from boiling water. It proved to be 2,6-oxy-4-phenyl-8-ethylpyrimidine, m.p. 210°-211°. The yellow substance was found to be a mixture largely of the pyrimidine hydrobromide, $Br[H_2NCONHC(C_6H_5):C(C_2H_5)CO]$ and unchanged pyrimidine, together with small quantities of bromopyrimidine and bromopyrimidine hydrobromide.

³The reaction bottle was rinsed out with a little chloroform which was then added to the chloroform filtrate.

40°), and the nearly white precipitate which formed was collected on a filter. This material (4 g.) melted with foaming at 120°-130°, solidified and remelted with decomposition at about 233°. It consisted largely of the bromopyrimidine hydrobromide with some pyrimidine hydrobromide. This material was suspended in water, boiled for a few minutes, treated with dilute ammonium hydroxide until the mixture was neutral, and then brought on a filter. After drying the material melted at 238°-242° with decomposition. By partial evaporation of the water filtrate crystals of the original pyrimidine, melting at 209°-211°, were obtained.¹ The solid melting at 238°-242° (2.8 g.) was combined with the compound melting at 233° (1 g.), and the whole was dissolved in a small amount of hot carbitol. On cooling the carbitol solution deposited crystals melting with decomposition at 250°-252°. When the carbitol filtrate was poured into cold water a further yield of the compound was secured.

The carbon tetrachloride filtrate, obtained by the filtration of the original reaction mixture, was evaporated on the steam bath to about one-fourth its volume. The white solid which separated out was collected on a filter and dried, 1.1 g. of material melting at 246°-248° being obtained. On recrystallization from carbitol and water a white powder was obtained which melted with decomposition at 251°-253°. This compound is identical with the compound melting at 250°-252° obtained above.²

The total yield of crude material obtained from 3.85 g. of 2,6-oxy-4-phenyl-5-ethylpyrimidine was 6.3 g. From this crude

¹The pyrimidine is soluble and the bromopyrimidine insoluble in hot water.

²Since the material decomposes at this temperature, the melting point depends considerably upon the speed with which the temperature of the bath is raised.

material about 2.9 g., or 55.4 per cent of the theoretical amount of pure monobromopyrimidine was obtained. The compound is soluble in warm dilute sodium hydroxide, hot carbitol and glacial acetic acid, insoluble in warm dilute hydrochloric acid, water, 33 per cent acetic acid, chloroform, alcohol and ether. Micro-analysis of the compound gave the following results: Calculated for $C_{12}H_{11}O_2N_2Br$: Br, 27.1; N, 9.5. Found: Br, 27.24, 26.97; N, 9.57, 9.49.

The bromination was also carried out in a three-necked flask fitted with a dropping funnel, a stirrer and a reflux condenser. The carbon tetrachloride suspension of the pyrimidine was stirred and kept gently boiling while the bromine, dissolved in carbon tetrachloride, was added to the mixture as rapidly as it was absorbed. With the 500 watt light placed within four or five inches of the flask the reaction was completed within thirty minutes. Considerable hydrogen bromide escaped through the condenser, to which a rubber tube was attached leading to the back of the hood. Smaller quantities of the hydrobromide were formed. From 2 g. of 2,6-oxy-4-phenyl-5-ethylpyrimidine a yield of 2.7 g. of crude material was obtained. From the crude material 0.45 g. of the original oxypyrimidine and 2.1 g. of the impure bromo-compound melting at 233° to 235° were obtained. This substance was combined with other similar material; hence the final yield of pure monobromopyrimidine by this method was not determined.

Behrend¹ first used oxidation by potassium permanganate to prove the structure of alkylated uracils. The bromopyrimidine was subjected to oxidation in an attempt to prove the position of the bromine atom in the compound. The reaction was carried out in

¹Loc. cit.

See also Terre, loc. cit.

the following manner: The bromopyrimidine (2 g.) was suspended in 200 cc. of water (at 40°) and dilute sodium hydroxide was slowly added to the mixture, with stirring, until solution was complete. A dilute solution of potassium permanganate (1.4 g. in 20 cc. of water) was gradually added to the cooled alkaline solution and the mixture was stirred for four hours at room temperature. The solid manganese dioxide which formed was removed by filtration and the clear filtrate was carefully neutralized with dilute hydrochloric acid. A light precipitate which formed could not be collected as it passed through the filter paper. The mixture was evaporated nearly to dryness on a steam bath. The material was then placed in a vacuum desiccator, over concentrated sulphuric acid, and left until it was dry. The dry material was extracted twice with 10 cc. portions of boiling absolute ethanol. A portion of the alcohol insoluble residue was dissolved in water, acidified with nitric acid and treated with silver nitrate solution. A heavy white precipitate formed which was soluble in ammonium hydroxide. A small amount of carbon tetrachloride was added to a portion of the water solution of the residue, chlorine water was then added to the mixture and the whole was shaken vigorously. The carbon tetrachloride remained colorless, thus proving the absence of bromine in the residue.

The alcoholic extract obtained above was evaporated to dryness and the residue thus obtained was extracted twice with small amounts of hot chloroform. The chloroform extract was evaporated to a small bulk and gradually poured into a relatively large volume of low boiling ligroin. The white precipitate which formed was collected on a filter and washed with a little ligroin. The compound melted and foamed at 130°-135°. It is very slightly soluble in cold or hot water giving a slightly acidic reaction. It is very soluble in alcohol, soluble in dilute sodium hydroxide

and insoluble in ether. A qualitative analysis proved the presence of nitrogen and bromine in the compound. Attempts to analyze the compound for bromine by the use of Parr's micro-bomb were unsuccessful as the material did not fuse properly. Micro-analysis for nitrogen gave the following result: Calculated for $\text{NH}_2\text{CONHCOC}_6\text{H}_4\text{Br}$: N, 11.52. Found: N, 11.85.

An attempt was made to prepare a bromobenzoic acid from the compound (m.p. 130° - 135°) by hydrolysis with hydrochloric acid, but no definite result was obtained. The few milligrams (40 to 50) of material available were refluxed for two hours with concentrated hydrochloric acid. The acid mixture was evaporated to dryness and extracted with ether. The ether extract was evaporated to dryness and the residue obtained was dissolved in a few drops of warm alcohol. Water was added to the alcoholic solution and the precipitate which formed was brought on a micro-filter. Barely enough material was obtained for a melting point determination. It melted from 155° to 167° . Meta-bromobenzoic acid melts at 155° : the ortho acid at 148° and the para acid at 251° . The identity of the compound is therefore still doubtful.

A consideration of the results of the oxidation of the bromopyrimidine seems to indicate that the bromine is substituted in the benzene nucleus. On the other hand the bromination of other similar pyrimidines always leads to the formation of 5-bromopyrimidines (see p.19). Further work will have to be done before the position of the bromine atom in 2,6-oxy-4-phenyl-5-ethyl bromopyrimidine can be positively determined.

The bromination of 2,6-oxy-4-phenyl-5-ethylpyrimidine was carried out with the expectation of obtaining 2,6-oxy-4-phenyl-5-ethyl-5-bromopyrimidine, $\text{NHCON:C}(\text{C}_6\text{H}_5)\text{CBr}(\text{C}_2\text{H}_5)\text{CO}$, which, it was

thought, might interact with magnesium ethyl bromide to form 2,6-oxy-4-phenyl-5,5-diethylpyrimidine, $\text{NHCON:C}(\text{C}_6\text{H}_5)\text{C}(\text{C}_2\text{H}_5)_2\text{CO}$. The Grignard reaction was carried out although the position of the bromine atom in the bromopyrimidine was not known for certain. A 50 cc. three-necked flask was fitted with a stirrer, a small dropping funnel and a reflux condenser. The apparatus was dried for two hours over an electric hot plate in a current of dry air. Magnesium ethyl bromide¹ was prepared in the three-necked flask from 0.42 g. of magnesium turnings, 12 cc. of dry, alcohol-free ether and 1.9 g. of ethyl bromide. The finely powdered bromo-pyrimidine (2 g.) was gradually added to the Grignard compound over a period of thirty minutes, the mixture being stirred vigorously meanwhile. When the bromopyrimidine came in contact with the Grignard reagent a vigorous evolution of gas occurred. The mixture was stirred and refluxed for two hours after the addition of the bromopyrimidine was completed, then cooled and poured into about 40 cc. of ice water containing 1 cc. of concentrated hydrochloric acid. The solid material present was brought on a filter and dried. It was found to consist largely of the original bromopyrimidine together with a small amount of material which did not melt at 300°. By the partial evaporation of the slightly acidic water filtrate a small amount of material was obtained which was identified as 2,6-oxy-4-phenyl-5-ethylpyrimidine (m.p. 211°). This may have been present in the bromopyrimidine as an impurity. No trace of a diethylpyrimidine was found.

¹See H. Gilman, "Organic Syntheses," XI, 98.

SUMMARY

1. The following methods of preparation of benzoylacetic ethyl ester were investigated:

- a. Claisen's method of condensation of ethyl benzoate and ethyl acetate.
- b. Claisen's method of condensation of benzoyl chloride and acetoacetic ester with subsequent hydrolysis of the condensation product to form benzoylacetic ester.
- c. Claisen's second method (b) as modified by Schriner and Schmidt. Claisen's second method (b) gave the best results and was selected for the preparation of the ester.

2. Benzoylacetic ethyl ester was ethylated in an alcoholic solution by the use of ethyl iodide and sodium ethylate. An average yield of 66.4 per cent of the theoretical yield of α -ethyl benzoylacetic ethyl ester was obtained.

3. The following new pyrimidines were prepared and studied:

- a. 2-Ethoxy-4-phenyl-6-oxypyrimidine,

$$\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)CH}_2\text{CO .}$$
- b. 2-Ethoxy-4-phenyl-5-ethyl-6-oxypyrimidine,

$$\text{N:C(OC}_2\text{H}_5\text{)N:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO .}$$
- c. 2,6-Oxy-4-phenyl-5-ethylpyrimidine,

$$\text{NHCON:C(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO .}$$
- d. 1,5-Ethyl-2-ethoxy-4-phenyl-6-oxypyrimidine,

$$\text{C}_2\text{H}_5\text{NC(OC}_2\text{H}_5\text{):NC(C}_6\text{H}_5\text{)CH(C}_2\text{H}_5\text{)CO .}$$
- e. 1,5-Ethyl-2,6-oxy-4-phenylpyrimidine,

$$\text{C}_2\text{H}_5\text{NCONHC(C}_6\text{H}_5\text{):C(C}_2\text{H}_5\text{)CO .}$$

4. After many attempts a monobromopyrimidine was prepared from 2,6-oxy-4-phenyl-5-ethylpyrimidine. No definite conclusion was reached regarding the position of the bromine atom in the bromopyrimidine from an examination of the oxidation products of the compound.

5. The bromopyrimidine was treated with magnesium ethyl bromide in an attempt to substitute an ethyl group for the bromine atom of the bromopyrimidine. The attempt was unsuccessful.

In conclusion the author wishes to express his appreciation to Dr. Stieglitz, under whose direction this problem was done, and to Dr. E. W. Lowe for his assistance.

